SYSTEM, APPARATUS AND METHOD FOR EVALUATING SAMPLES OR ANALYTES USING A POINT-OF-CARE DEVICE

RELATED APPLICATIONS

[0001] This patent application claims priority to U.S. provisional patent application Ser. No. 61/541,559 filed on Sep. 30, 2011 entitled "Distributed Handheld Molecular Diagnostic Point-of-Care Device", which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates generally to the field of medical diagnostic and health care systems, and more particularly, to a system, apparatus and method for evaluating samples or analytes using a point-of-care device.

BACKGROUND OF THE INVENTION

[0003] DNA and other molecular level analysis can detect genetic variations, which comprise single nucleotide polymorphisms (SNPs) and structural variations (SVs). These can be further divided into microscopic (larger than 3 Mb) and submicroscopic variations. SVs can be defined as all genomic changes that are not single base-pair substitutions and include insertions, deletions, inversions, duplications and translocations of DNA sequences, as well as copy number variants (CNVs). Starting in the mid 1980s, the process of DNA extraction, testing, and analysis was laborious and required months of time utilizing specialized equipment in research laboratories to generate and analyze the data. With the advent of the polymerase chain reaction (PCR), the process for obtaining DNA-based information became faster and more efficient. While PCR technology has greatly simplified the process, DNA analysis today is performed by highly trained technicians in either research or clinical laboratories. The process generally requires the extraction of the DNA from the biological sample followed by PCR amplification. The extraction step can be accomplished using an automated DNA extractor, a highly specialized piece of equipment, which can be bench top-sized or larger. Manufacturers of these devices include Autogen, Invitrogen, and Promega. The extraction step can also be done manually by a technician using a kit (e.g., a Qiagen kit). Each sample must be extracted separately, and the manual extraction step is a source of potential contamination of the sample. Once the DNA has been extracted, the DNA is amplified using a thermal cycler or thermal cycler as a separate piece of equipment from the extractor. Manufacturers of thermal cyclers include Eppendorf, Applied Biosystems, BioRad, and Hitachi-300. Detection of PCR products is usually accomplished via fluorescence. Once detection has occurred, there needs to be an additional step to analyze and interpret the results for clinical relevance. For example, the relation of single nucleotide polymorphisms (SNPs) in a DNA sample to a predicted drug response for a patient requires a detailed bioinformatic analysis step, which often can take 14 days or longer for results to be received.

[0004] In addition to PCR, there are a number of other technologies for DNA analysis, all of which require highly trained technicians in a clinical or research laboratory setting utilizing specialized equipment. Microarray technology provides new analytical devices that allow the parallel and simultaneous detection of several thousands of probes within one sample. Microarrays, sometimes called DNA chips, are widely used in gene expression analysis, genotyping of individuals, analysis of point mutations and singlenucleotide polymorphisms (SNP), as well as other genomic or transcriptomic variations. For microarray technologies, a separate device for detection is needed (instead of a thermal cycler) to detect fluorescence. Different types of microarrays include printed arrays, in situ-synthesized oligonucleotide arrays (includes Roche NimbleGen, Affymetrix GeneChip, and Agilent), high-density bead arrays (includes Illumina BeadArray), electronic arrays (includes Nanogen NanoChip), and suspension bead arrays (includes Luminex xTAG). Microarrays are plagued by false positives and questionable quantifications, and the data require a separate and complex analysis step. Additionally, DNA microarrays have some problems in terms of reproducibility and reliability due to the fact that the DNA probes are fixed on electrodes.

[0005] Another technique is fluorescence in situ hybridization (FISH). FISH allows the mapping of specific DNA sequences at high resolution. However, it is time-consuming and labor-intensive, which limits its application as a genome-wide variation screening tool. FISH can be used to detect microscopic structural variations larger than 3 Mb, including visible chromosomal heteromorphisms, reciprocal translocations, deletions, duplications, insertions and inversions.

[0006] More recently, lab-on-a-chip technologies are compact in size and enable low sample volumes (nanoliter) and short analysis time (less than 10 sec to complete one PCR cycle, 370 sec for completing the whole quantification process). Some disadvantages are detection limits, quantification uncertainties, and melting analysis ability of chip prototypes. Other technologies include multiplex amplifiable probe hybridization (MAPH) and multiplex ligation-dependent probe amplification (MLPA), which can efficiently detect the specific changes at 50-100 genomic loci in a single experiment. MAPH is fast and cost-effective in detecting small genomic changes, but the limited multiplicity owing to gel-based detection is a major drawback. MAPH combined with microarrays increases the detection throughput.

[0007] PCR microfluidics enables large numbers of parallel amplification analyses on a single chip and can produce more accurate information and greater understanding necessary for some particular bioassays, which, however, are difficult, unpractical, or even impossible to perform on a macro-scale PCR device. Besides, single molecule PCR can be easily performed in PCR microfluidics, starting with a single-copy sequence in the PCR mixture. Much smaller PCR vessels can increase resolution while reducing the overall size of the PCR device, but effects related to the non-specific adsorption of biological samples to the surfaces of the vessel may become significant as a result of the increased Surface-to-Volume Ratio (SVR) upon miniaturization, which may inhibit PCR amplification. As is seen from the development history of PCR microfluidics, another "bottleneck" blocking the realization of a truly integrated DNA analyzer may be a portable detection module for on-line PCR product detection. The most common detection scheme is off-line or on-line CE separation of the PCR product, usually followed by laser induced fluorescence detection or in some cases by EC detection. However, optical detection systems are difficult to miniaturize onto a monolithic microanalytical system. Furthermore, the electrophoretic separation and detection technique cannot provide data on the sequence of the PCR product since it mainly serves to separate DNA fragments of different sizes